Review Article

Chronic obstructive pulmonary disease lost in translation: Why are the inhaled corticosteroids skeptics refusing to go?

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Abstract:

A survey of pulmonologists attending a clinical meeting of the Saudi Thoracic Society found that only 55% of responders considered that inhaled corticosteroids (ICS) had a positive effect on quality of life in Chronic Obstructive Pulmonary Disease (COPD). Why the divergence of opinion when all the guidelines have concluded that ICS improve quality of life and produce significant bronchodilation? ICS unequivocally reduce the rate of exacerbations by a modest 20%, but this does not extend to serious exacerbations requiring hospitalization. Bronchodilatation with ICS is now documented to be restricted to some phenotypes of COPD. Withdrawal of ICS trials reported a modest decline of FEV_1 (<5%) in half the studies and no decline in the other half. In spite of the guidelines statements, there is no concurrence on whether ICS improve the quality of life and there is no conclusive evidence that the combination of long-acting ß2 agonists (LABA) with ICS is superior to LABA alone in that regard. The explanation for these inconclusive results may be related to the fact that COPD consists of three different phenotypes with divergent responses to LABA and ICS. Therapy tailored to phenotype is the future for COPD.

Key words: COPD, inhaled corticosteroids, phenotyping

We surveyed pulmonologists attending a scientific meeting of the Saudi Thoracic Society on whether the use of inhaled corticosteroids (ICS) results in improvement of quality of life in Chronic Obstructive Pulmonary Disease (COPD). Only 55% responded affirmatively while 45% thought ICS had no effect on quality of life. Why this divergence of opinion when all major guidelines concluded that ICS improve quality of life and produce significant spirometric improvement in COPD? The skepticism is not limited to Saudi pulmonologists: Studies and surveys document large differences in ICS use between various countries. Also, medical journals are still airing dissenting views that challenge the main stream belief in ICS in COPD as enshrined in the guidelines. Why the confidence gap?

Inhaled corticosteroids and COPD

A Google search for COPD and corticosteroids yielded 685 000 results! A PubMed search yielded 2 307 results (including 768 reviews). Given this staggering amount of research and reviews, it is surprising that the role of ICS in COPD is still controversial. Table 1 summarizes the areas of controversy.

The position of various scientific bodies on the role of inhaled corticosteroids

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) states that ICS improve symptoms, lung function, and quality of life, and reduce the frequency of exacerbations (Evidence A).[3] Withdrawal from treatment with ICS–GOLD concluded - may lead to exacerbations in some patients and that regular treatment with ICS neither modify the long-term decline of FEV_1 nor mortality (Evidence A).[3] When it comes to the combination, ICS/long-acting ß-2 agonists (LABA) GOLD states that a large prospective clinical trial failed to demonstrate a significant effect on mortality, but a subsequent meta-analysis found that combination therapy may reduce mortality (Evidence B).[3] The US Food and Drug Administration (FDA) approved the combination of ICS/LABA for the reduction of exacerbations and for improving the FEV_1 above

Table 1: Controversy of the role of ICS in COPD

Areas where ICS* is widely (but not universally) accepted	Areas where the effect of ICS is still debated
Modest reduction of exacerbations	ICS produce a bronchodilator effect
Withdrawal of ICS causes increased exacerbation rates	Improvement in the quality of life
Do not slow deterioration of FEV_1	Abrupt withdrawal of ICS trigger spirometric deterioration
No reduction of mortality	
Small but significant increase of the risk of pneumonia without corresponding increase of mortality (ICS)[1,2]	

*ICS = Inhaled corticosteroids

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what LABA could achieve. The FDA took the further step of approving a role for COPD not only "with chronic bronchitis but also emphysema or both conditions."[4]

The reduction of exacerbations by ICS is marginal compared with LABA and does not extend to exacerbations requiring hospitalization.

In the Torch study, one of the best designed and frequently quoted studies, the mean annual exacerbation rates (no/pt/yr) were as follows [Table 2]:[5]

As exacerbations requiring hospitalization are disproportionately responsible for financial cost and mortality, it is clear that the impact of therapy is not huge. Another large study used requiring oral corticosteroids as a marker of severity of exacerbation; the rates were 1.14 (placebo), 0.91 (formoterol), 0.87 (budesonide), and 0.63 (combination).[6] These findings—unlike those of the Torch Study—lend support to the theory that ICS and LABA are synergistic to each other's effect, with the reduction of exacerbation with the combination greater than with either drug alone. However, that study used patients who smoked as little as 10 packs/year, where they are likely to be suffering from irreversible asthma and not COPD.[7] In the Tristan study, the exacerbation rate was 1.3 (P), 1.04 (LABA), 1.05 (ICS), and 0.97 (Comb.).[8] Although a statistically significant difference exists between the LABA and combination arms, the difference was of little practical significance (0.07 exacerbations per year). Szafranski *et al.* reported rates of 1.87, 1.84, 1.59, and 1.42, respectively.[9] Calverley *et al.* recently reported no difference between LABA and the combination.[10]

In conclusion, the effect of combination is only marginally better than LABA (and absent in some studies) but does not extend to hospitalization. A recent meta-analysis found that the rate of exacerbations requiring oral corticosteroids was 17.5% with the combination and 20.1% with LABA.[11] The same meta-analysis found no significant difference in exacerbations requiring hospitalization.[11] This supports the findings of the TORCH study.

Withdrawal of ICS is associated with a small risk of increased exacerbations. Interestingly, a recent study found that the risk of exacerbations in COPD is associated with sputum eosinophilia, long duration of symptoms, and smoking ≤ 40 packs/year.[12] Other studies documented that these features are indicative of a steroid-responsive phenotype of COPD, or a diagnosis of irreversible asthma.[7,13,14] As discussed below, phenotyping can predict responsiveness to ICS.

The effect of ICS and LABA + ICS on quality of life is not consistent and usually below the level of clinical relevance.

We reviewed 11 studies which reported on changes in health-related quality of life of which 10 had a duration of 12 months or more.[5,6,8-10,15-20] LABA were associated with deterioration of quality of life in two studies and with improvement in six other studies. ICS were associated with deterioration in one study and improvement in five other studies (none of them above the four-point threshold of clinical relevance). The combination of LABA + ICS produced the same pattern: two studies showed deterioration of quality of life, and another six showed improvement. In only three of these, the improvement was above the 4-point threshold. In one of these, the LABA + ICS produced an impressive improvement of – 7.5.[6] However, the improvement was against placebo (and not baseline); the placebo itself had registered a deterioration of about 4.5 units.[6] The real change (from baseline) after 12 months of therapy with LABA + ICS was less than 3 points [Table 3].[6]

Table 2: The mean annual exacerbation rates of COPD in torch study

	Placebo	Salmeterol	Fluticasone	Salm + Flut
Moderate or severe exacerbations (no./pt./year)	1.13	0.97	0.93	0.85
Rate ratio (95% CI) Versus placebo		0.85 (0.78-0.93)	0.82 (0.76-0.89)	0.75 (0.69-0.81)
Severe requiring hospitalization (no./pt./year)	0.19	0.16	0.17	0.16
Rate ratio (95% CI) Versus placebo		0.82 (0.69-0.96)	0.88 (0.74-1.03)	0.83 (0.71-0.98)

Table 3: Studies showed change in St. George's Respiratory Questionnaire in COPD

Study	Change In SGRQ			
	Placebo	LABA	ICS	LABA + ICS
Torch 2007[5] n = 6112	+ 0.2	-0.8	-1.8	-3
Tristan 2003[8] n = 1465	-2.30	-3.4	-3.1	-4.5
Szafranski 2003 *et al*,[9] n = 812	-0.03	-3.6	-1.9	-3.9
Rennard 2009[19] n = 1964	-1.50	2.90		-3.90
Anzueto 2009[20] n = 797		+3.28		+2.49

SGRQ = St. george's respiratory questionnaire

A large number of studies showed ICS (alone or in combination with LABA) to improve FEV_1. Why should that be the case?

A large bulk of COPD studies deal with the effect of ICS on pulmonary function and have reported a significant positive effect on FEV_1.[10,21-24] Some of these studies reported average rise of FEV_1 of 29% in the "reversible" group of COPD patients following therapy with LABA + ICS.[21,22] Fluticasone and budesonide were the drugs of choice used in these studies but claims were made for other corticosteroids.[10] The explanation given for a "bronchodilator" effect of ICS is their anti-inflammatory effect. The claims for ICS contradict all published evidence for the following reasons:

1. About a dozen studies reported on the effect of ICS on inflammatory cells in sputum, bronchial biopsy, or bronchi alveolar lavage of COPD patients. With the exception of two studies (with marginal reduction in cells), all demonstrated no reduction of inflammatory cells, particularly neutrophils.[14,25-30] Also, ICS had no effect on inflammatory markers or protease—antiprotease balance.[26,27]

2. In both asthma and COPD, multiple inflammatory genes are activated as a result of acetylation of core histones around which DNA is wound. This facilitates gene transcription and synthesis of inflammatory mediators. Histone deacetylase 2 are recruited by corticosteroids to switch off this process.[31,32] Barnes hypothesized that oxidative stress in COPD impair the function of HDAC 2 and render the condition unresponsive to corticosteroids even after cessation of smoking.[31,32] The drugs proposed to reverse the steroids unresponsiveness—like antioxidants, theophylline, nortriptyline, or phosphoinositide – three – Kinase inhibitors although exciting are still experimental or unproven in large clinical trials.[33-35]

We suggested in 2004 that one of the largest studies demonstrating a bronchodilator effect of ICS of COPD had inadvertently included patients with asthma.[36] This was based on the fact that patients aged 40 to 49 years and patients with previous (but not current) history of asthma were included.[36] Also, half the patients were "reversible" with 30% rise of FEV_1 in response to inhaling 400 µcg of salbutamol.[22] Although short-term response to Salbutamol is unreliable in differentiating asthma and COPD, patients with the latter condition have generally a much lower FEV_1 response. Lastly, the improvement of FEV_1 was manifest only after 24 hours of ICS therapy, a behavior not compatible with asthma not COPD outside exacerbations.[22]

We had to wait a decade to build evidence that whenever a form of phenotyping was used, COPD was split into two entities: steroid-responsive and non-responsive. Table 4 summarizes some of these studies.

The old concept of ''chronic bronchitis'' form of COPD free of emphysema (and represented by blue bloaters) is not only challenged by CT scanning, but also postmortem studies.[41,42] Although pink puffers and blue bloaters show clinical differences, they do not represent major difference in the degree of emphysema at death.[42] The above studies and others show that the following phenotypes are not ICS or prednisolone responders: bronchial histology showing no thickening of basement membrane, lack of eosinophilia in sputum, short duration of smoking, reduced carbon monoxide diffusion capacity (DLCO), or predominant emphysema by CT scanning.[7,13,14,37-39,43] The opposite is also true: eosinophilic COPD (20 - 40% of all cases), uniform thickening of basement membrane, or patients in the lowest percentile for CT scan-diagnosed emphysema (even if severely obstructed) have many features of asthma including significant responsiveness to β2-agonists and corticosteroids.[7,13,14,37-39,43,44]

Whenever phenotyping was used (CT, bronchial biopsy, sputum eosinophila. . . etc), COPD splits into a steroid-responsive and steroid-unresponsive groups. Some workers have recently expressed the view that treatment should be targeted to the phenotype of COPD whether asthma, mixed COPD, or predominantly emphysema.[45,46]

Spirometric decline on withdrawal of inhaled corticosteroids

Four studies reported on the effect of withdrawal of corticosteroids on FEV_1 and produced contradictory results. Two studies documented decline of FEV_1 but another two found no decline.[47-50] In one of the studies although the mean FEV1 significantly dropped, the decline occurred in some but not all patients, and some patients had normal DLCO.[47]

Table 4: Summary of studies showing the effect of phenotyping on response to inhaled corticosteroids in COPD

Paper	Method of phenotyping/ drug tested	Main results
Chanez *et al* (1996)[37]	Bronchial biopsy/oral prednisolone	12/25 patients with > 12% reversibility of FEV_1 after prednisolone had histology of asthma
Brightling *et al* (2000)[13] [Figure 1]	Sputum eosinophila/oral prednisolone versus placebo	Significant rise of FEV_1, shuttle walk distance, and health status (CRQ) only with eosinophilia > 3%
Brightling *et al* (2005)[14] [Figure 2]	Sputum eosinophilia/inhaled mometasone versus placebo	Significant (mean 110 ml) rise of post-bronchodilator FEV_1 only in the most eosinophilic tertile. No significant change of health status (CRQ) in any tertile.
Fujimoto *et al* (1999)[38]	Sputum eosiophilia/ oral prednisolone	Rise of FEV_1 correlated with eosinophils (not neutrophils) percentage in sputum.
Lee *et al* (2010)[39]	CT scan (computerized score/Fluticasone + Salmeterol or Budesonide + formoterol for 3 months	Emphysema – dominant subtype showed no improvement of FEV_1 (32 ml) or dyspnea scale (0.16). However, patients with severe obstruction without emphysema (mean FEV_1 37% pred.) had normal mean DLCO (85.6% pred.) and improved FEV_1 by 207 ml and dyspnea by – 0.68
Al-Kassimi *et al* (2011)[7]	CT scan (Qualitative visual), bronchial biopsy, and hypercapneic respiratory failure to classify into COPD and irreversible asthma/Budesomide + Formoterol for 12 months	COPD patients showed no significant rise of FEV_1 while irreversible asthma group improved their mean FEV_1 by 350 ml.
Al-Kassimi *et al* (2011)[40]	CT scan, bronchial biopsy, ABG,KCO/Budesonide + Formoterol	Abrupt withdrawal of budesonide produced no significant drop of FEV_1 in COPD after excluding irreversible asthma cases
Fujimoto *et al* (2006)[41]	CT scan (visual semi-quantitative) to detect emphysema and bronchial wall thickening (BWT) • No or little emphysema (A phenotype) 22.7% • Emphysema without BWT (E phenotype) 51.7% • Emphysema with BWT (M phenotype) 25.6%	A Phenotype: 18% are never smokers/most patients had normal DLCO/ Salbutamol reversibility significant (13.1 %) M phenotype: practically all smokers DLCO (61.6%+2.8)/ salbutamol reversibility significant (16.8%) E Phenotype: practically all smokers (DLCO 49.3% +2.1/ mean reversibility Salbutamol not significant (10.7%)

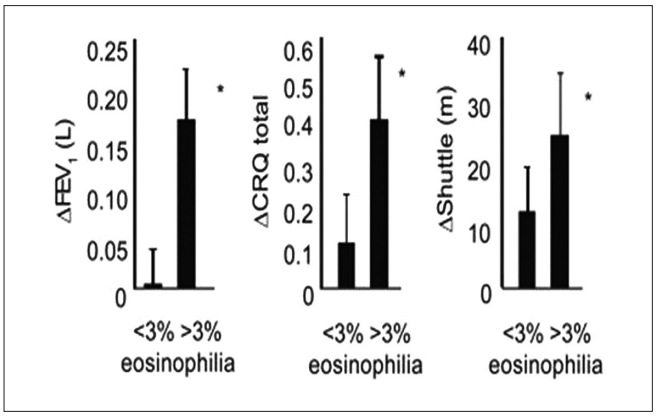

Figure 1: Effect of short time prednisolone on FEV_1, chronic respiratory questionnaire (CRQ), and incremental shuttle distance (ISD) in correlation with sputum eosinophilia[13]

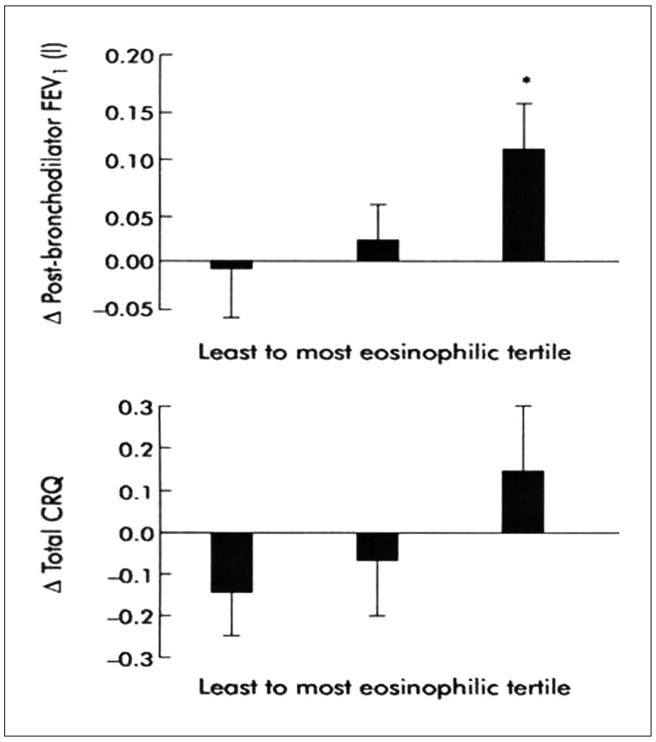

Figure 2: Effect of inhaled mometasone on FEV_1 and chronic respiratory questionnaire (CRQ) in correlation with sputum eosinophilia[14]

The discrepancy between patients may represent the effect of studying a mixed group of irreversible asthma and COPD. Al-Kassimi *et al*. reported no spirometric deterioration in a group selected for the following proper COPD phenotype: panlobular emphysema on CT scan, chronic hypercapneic respiratory failure (never described in stable asthma outside exacerbations), bronchial histology indicative of COPD, and low coefficient for carbon monoxide diffusion (KCO).[40]

Overall view of inhaled corticosteroids in chronic obstructive pulmonary disease

We believe that the contradictory and inconclusive results obtained from ICS trials in COPD (outside reduction of exacerbations) reflects the heterogeneous nature of COPD and the relative weight of irreversible asthma cases in the COPD population under study. A large meta-analysis concluded that ICS did not slow down the rate of decline of FEV_1.[51] A similar meta-analysis reached a different conclusion and reported a slowdown of FEV_1 by 7.7 ml/year.[52] The second meta-analysis was tipped in favor of ICS by including one study which made only a small contribution to the meta-analysis and which was published as an abstract not a peer reviewed Journal article.[52,53] In a large (47 primary studies) Cockrane Database review, use of ICS resulted in a small improvement of FEV_1, in some but not all studies.[54] This again highlights the heterogenicity of COPD. Barnes concluded that only some COPD patients with "concomitant asthma" may benefit from ICS.[55] Regrettably, the atmosphere of confusion has resulted in many practitioners prescribing ICS outside the accepted GOLD recommendation of $FEV_1 < 50\%$ and frequent exacerbations. Only a minority of COPD cases belong to that group. In the average patient, ICS would prevent 0.26 exacerbation per year (or one attack every four years), not extending to attacks requiring hospitalization.[54] More importantly, the guidelines should spell the bitter truth: COPD is not one entity that can be managed in the same way! Phenotyping should influence therapy with ICS and must be incorporated in clinical practice. The recently expressed calls for targeting treatment to the phenotype of COPD should be heeded.[45,46]

References

1. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: A systematic review and meta-analysis. JAMA 2008;300:2407-16.
2. Singh S, Loke YK. Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: a critical review and update. Curr Opin Pulm Med 2010;16:118-22.
3. Global Initiative for chronic obstructive pulmonary disease. Updated Dec. 2011. Available from: http://www.goldcopd.org [Last accessed on 2012 Feb 2].
4. FDA approves Fluticasone/Salmeterol Inhalation powder for reduction of COPD exacerbation, 2008. FDA approves Budesonide/Formoterol Fumarate Dihydrate for COPD, 2009. Available from: http://www.docguide.com [Last accessed on 2011 June 28th].
5. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, *et al*. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.
6. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and fromoterol in chronic obstructive pulmonary disease. Eur Respir J 2003;22:912-9.
7. Al-Kassimi FA, Abba AA, Al-Hajjaj MS, Alhamad EH, Raddaoui E, Shaikh SA. Asthma masquerading as chronic obstructive pulmonary disease: A study of smokers fulfilling the GOLD definition of chronic obstructive pulmonary disease. respiration 2011;82:19-27.
8. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, *et al*. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial. Lancet 2003;361:449-56.
9. Szafranski W, Cukier A, Ramirez A, Menga G, Sansores S, Nahabedian S, *et al*. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003;21:74-81.

10. Calverley PM, Kuna P, Monsó E, Costantini M, Petruzzelli S, Sergio F, *et al*. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. Respir Med 2010;104:1858-68.
11. Rodrigo GJ, Castro-Rodriguez JA, Plaza V. Safety and efficacy of combined long-acting beta-agonists and inhaled corticosteroids vs long-acting beta-agonists monotherapy for stable COPD: a systematic review. Chest 2009;136:1029-38.
12. Liesker JJ, Bathoorn E, Postma DS, Vonk JM, Timens W, Kerstjens HA. Sputum inflammation predicts exacerbations after cessation of inhaled corticosteroids in COPD. Respir Med 2011;105:1853-60.
13. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, *et al*. Sputum eosinophila and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomized controlled trial. Lancet 2000;356:1480-5.
14. Brightling CE, McKenna S, Hargadon B, Birring S, Green R, Siva R, *et al*. Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. Thorax 2005;60:193-8.
15. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297-303.
16. Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone proprionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;175:144-9.
17. Calverley PM, Rennard S, Nelson HS, Karpel JP, Abbate EH, Stryszak P, *et al*. One year treatment with monetasone furoate in chronic obstructive pulmonary disease. Respir Res 2008;9:73.
18. Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. Respir Med 2008;102:1099-108.
19. Rennard SI, Tashkin DP, McElhattan J, Goldman M, Ramachandran S, Martin UJ, *et al*. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: Results from a 1-year randomized controlled clinical trial. Drugs 2009;69:549-65.
20. Anzueto A, Ferguson CT, Feldman G, Chinsky K, Seibert A, Emmett A, *et al*. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. COPD 2009;6:320-9.
21. Mahler DA, Wire P, Horstman D, Chang CN, Yates J, Fischer T, *et al*. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus devise in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166:1084-91.
22. Hanania NA, Darken P, Horstman D, Reisner C, Lee B, Davis S, *et al*. The efficacy and safety of fluticasone propionate (250 mg)/salmeterol (50 mg) combined in the Diskus Inhaler for the treatment of COPD. Chest 2003;124:834-43.
23. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, *et al*. Trial of Inhaled Steroids And long-acting beta agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: A randomized controlled trial. Lancet 2003;361:449-56.
24. Tashkin DP, Rennard SI, Martin P, Ramachandran S, Martin UJ, Silkoff PE, *et al*. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: Results of a 6-month randomized clinical trial. Drugs 2008;68:1975-2000.
25. Saha S, Brightling CE. Eosinophilic airway inflammation in COPD. Int J COPD 2006:1:39-47.
26. Keatings VM, Jatakanon A, Worsdell YM, Barnes PJ. Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. Am J Respir Crit Care Med 1997;155:542-8.
27. Culpitt SV, Maziak W, Loukidis S, Nightingale JA, Matthews JL, Barnes PJ. Effect of high dose inhaled steroid on cells, cytokines, and proteases in induced sputum in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160:1635-9.
28. Loppow D, Schleiss MB, Kanniess F, Taube C, Jörres RA, Magnussen H. In patients with chronic bronchitis a four week trial with inhaled steroids does not attenuate airway inflammation. Respir Med 2001;95:115-21.
29. Gizycki MJ, Hattotuwa KL, Barnes N, Jeffery PK. Effects of fluticasone propionate on inflammatory cells in COPD: an ultrastructural examination of endobronchial biopsy tissue. Thorax 2002;57:799-803.
30. Hattotuwa KL, Gizycki MJ, Ansari TW, Jeffery PK, Barnes NC. The effects of inhaled fluticasone on airway inflammation in chronic obstructive pulmonary disease: A double-blind, placebo-controlled biopsy study. Am J Respir Crit Care Med 2002;165:1592-6.
31. Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. Br J Pharmacol 2006;148:245-54.
32. Barnes PJ. Targeting the epigenome in the treatment of asthma and chronic obstructive pulmonary disease. Am Thorac Soc 2009;6:693-6.
33. Barnes PJ, Ito K, Adcock IM. Corticosteroid resistance in chronic obstructive pulmonary disease: inactivation of histone deacetylase. Lancet 2004;363:731-3.
34. Marwick JA, Chung KF. Glucocorticoid insensitivity as a future target of therapy for chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2010;5:297-309.
35. Mercado N, To Y, Ito K, Barnes PJ. Nortriptyline reverses corticosteroid insensitivity by inhibition of phosphoinositide-3-kinase-ō. J Pharmacol Exp Ther 2011;337:465-70.
36. El-Kassimi FA. Differentiating asthma and COPD patients. Chest 2004;126:654-5.
37. Chanez P, Vignola AM, O'Shaugnessy T, Enander I, Li D, Jeffery PK, *et al*. Corticosteroid reversibility in COPD is related to features of asthma. Am J Respir Crit Care Med 1997;155:1529-34.
38. Fujimoto K, Kubo K, Yamamoto H, Yamaguchi S, Matsuzawa Y. Eosinophilic inflammation in the airway is related to Glucocorticoid. Reversibility in patients with pulmonary emphysema. Chest 1999;115;697-702.
39. Lee JH, Lee YK, Kim EK, Kim TH, Huh JW, Kim WJ, *et al*. Responses to inhaled long-acting beta-agonist and corticosteroid according to COPD subtype. Respir Med 2010;104:542-9.
40. Al-Kassimi FA, Al-Hajjaj MS, Alhamad ES, Abba AA, Raddaoui E, Shaikh SA. Abrupt withdrawal of Inhaled Corticosteroids in COPD Does not Produce Spirometric Deterioration: Role of Phenotyping. Gulf Thoracic Conference proceedings, published in Ann Thorac Med, 2011;6:159-83.
41. Fujimoto K, Kitaguchi Y, Kubo K, Honda T. Clinical analysis of chronic obstructive pulmonary disease phenotypes classified using high-resolution computed tomography. Respirology 2006;11:731-40.
42. Mitchell RS, Stanford RE, Johnson JM, Silvers GW, Dart G, George MS. The morphologic features of the bronchi, bronchioles, and alveoli in chronic airway obstruction: A clinicopathologic study. Am Rev Respir Dis 1976;114:137-45.
43. Fabbri LM, Romagnoli M, Corbetta L, Casoni G, Busljetic K, Turato G, *et al*. Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;167:418-24.
44. Hersh CP, Jacobson FL, Gill R, Silverman EK. Computed tomography phenotypes in severe, early-onset chronic obstructive pulmonary disease. COPD 2007;4:331-7.
45. Fingleton J, Weatherall M, Beasley R. Towards individualized treatment in COPD. Thorax 2011;66:363-4.

46. Shirtcliffe P, Weatherall M, Travers J, Beasley R. The multiple dimensions of airways disease: targeting treatment to clinical phenotypes. Curr Opin Pulm Med 2011;17:72-8.
47. O'Brien A, Russo-Magno P, Karki A, Hiranniramol S, Hardin M, Kaszuba M, *et al*. Effects of withdrawal of inhaled steroids in men with severe irreversible airflow obstruction. Am J Respir Crit Care Med 2001;164:365-71.
48. Van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, Herwaarden C van. Effect of discontinuation of inhaled corticosteroids in patients with Chronic Obstructive Pulmonary Disease. The COPE study. Am J Respir Crit Care Med 2002;166:1358-63.
49. Wouters EF, Postma DS, Fokkenst B, Hop WCJ, Prins J, Kuipers AF, *et al*. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomized controlled trial. Thorax 2005;60:480-7.
50. Choudhury AB, Dawson CM, Kilvington HE, Eldridge S, James WY, Wedzicha JA, *et al*. Withdrawal of inhaled corticosteroids in people with COPD in primary care: A randomized controlled trial. Respir Res 2007;6:93.
51. Highland KB, Strange C, Heffner JE. Long-term effects of inhaled corticosteroids on FEV_1 in patients with chronic obstructive pulmonary disease. A meta-analysis. Ann Intern Med 2003;138:969-73.
52. Sutherland ER, Allmers H, Ayas NT, Venn AJ, Martin RJ. Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis. Thorax 2003;58:937-41.
53. Derenne JP. Effects of high-dose inhaled beclomethasone on the rate of decline in FEV_1 in patients with chronic obstructive pulmonary disease: Results of a 2 year prospective multicentre study. Am J Respir Crit Care Med 1995;151:A463.
54. Yang IA, Fong KM, Sim EH, Black PN, Lasserson TJ. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2007;18:CD002991.
55. Barnes PJ. Inhaled corticosteroids in COPD: A controversy. Respiration 2010;80:89-95.

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